

10/04 9556

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NEWS 12 FEB 27 New STN AnaVist pricing effective March 1, 2006
NEWS 13 FEB 28 MEDLINE/LMEDLINE reload improves functionality
NEWS 14 FEB 28 TOXCENTER reloaded with enhancements
NEWS 15 FEB 28 REGISTRY/ZREGISTRY enhanced with more experimental spectral
property data
NEWS 16 MAR 01 INSPEC reloaded and enhanced
NEWS 17 MAR 03 Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 18 MAR 08 X.25 communication option no longer available after June 2006
NEWS 19 MAR 22 EMBASE is now updated on a daily basis
NEWS 20 APR 03 New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 21 APR 03 Bibliographic data updates resume; new IPC 8 fields and IPC
thesaurus added in PCTFULL
NEWS 22 APR 04 STN AnaVist \$500 visualization usage credit offered
NEWS 23 APR 12 LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS 24 APR 12 Improved structure highlighting in FQHIT and QHIT display
in MARPAT
NEWS 25 APR 12 Derwent World Patents Index to be reloaded and enhanced during
second quarter; strategies may be affected

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 13:26:40 ON 17 APR 2006

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'CAPLUS' ENTERED AT 13:26:52 ON 17 APR 2006

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 17 Apr 2006 VOL 144 ISS 17

FILE LAST UPDATED: 16 Apr 2006 (20060416/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

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=> fiel caplus embase biosis medline

FIEL IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.

For a list of commands available to you in the current file, enter

"HELP COMMANDS" at an arrow prompt (=>).

=> file caplus embase biosis medline

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.46

0.67

FILE 'CAPLUS' ENTERED AT 13:27:21 ON 17 APR 2006

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

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FILE 'EMBASE' ENTERED AT 13:27:21 ON 17 APR 2006

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FILE 'BIOSIS' ENTERED AT 13:27:21 ON 17 APR 2006

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FILE 'MEDLINE' ENTERED AT 13:27:21 ON 17 APR 2006

=> s bisphosphonate?

L1 16258 BISPHOSPHONATE?

```

=> s bone growth
L2      16524 BONE GROWTH

=> L1 and L2
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s L1 and L2
L3      162 L1 AND L2

=> dup rem
ENTER L# LIST OR (END):L3
PROCESSING COMPLETED FOR L3
L4      98 DUP REM L3 (64 DUPLICATES REMOVED)

=> s L4 and (AY<2001 or PY<2001 or PRY<2001)
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
L5      48 L4 AND (AY<2001 OR PY<2001 OR PRY<2001)

=> s L5 and fracture
L6      19 L5 AND FRACTURE

=> s fracture?
L7      466145 FRACTURE?

=> s zoledronate
L8      754 ZOLEDRONATE

=> s L8 and L7
L9      126 L8 AND L7

=> dup rem L9
PROCESSING COMPLETED FOR L9
L10     83 DUP REM L9 (43 DUPLICATES REMOVED)

=> s L10 and (AY<2001 or PY<2001 or PRY<2001)
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
'2001' NOT A VALID FIELD CODE
L11     13 L10 AND (AY<2001 OR PY<2001 OR PRY<2001)

=> d L6 1-19 ibib abs

L6  ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:      2005:362895  CAPLUS
DOCUMENT NUMBER:       142:404295
TITLE:                 Inhibitors of proteasomal activity for stimulating
                        bone and hair growth
INVENTOR(S):           Mundy, Gregory R.; Garrett, I. Ross; Rossini, Jorge
                        Gianni
PATENT ASSIGNEE(S):    Osteoscreen, Inc., USA
SOURCE:                U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 421,545.
                        CODEN: USXXAM
DOCUMENT TYPE:         Patent

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LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6884769	B1	20050426	US 2000-558973	20000425 <--
US 6462019	B1	20021008	US 1998-113947	19980710 <--
US 6410512	B1	20020625	US 1999-361775	19990727 <--
US 6902721	B1	20050607	US 1999-421545	19991020 <--
CA 2385958	AA	20010426	CA 2000-2385958	20001020 <--
WO 2001028579	A2	20010426	WO 2000-US41360	20001020 <--
WO 2001028579	A3	20010920		
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 2001021183	A5	20010430	AU 2001-21183	20001020 <--
EP 1221962	A2	20020717	EP 2000-984583	20001020 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003528039	T2	20030924	JP 2001-531407	20001020 <--
EP 1477180	A1	20041117	EP 2004-15639	20001020 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2006089498	A2	20060406	JP 2005-330878	20051115 <--
AU 2005246961	A1	20060119	AU 2005-246961	20051220 <--
PRIORITY APPLN. INFO.:				
			US 1998-113947	A2 19980710 <--
			US 1999-361775	A2 19990727 <--
			US 1999-421545	A2 19991020 <--
			JP 2000-558808	A3 19990709 <--
			US 2000-558973	A 20000425 <--
			AU 2001-21183	A3 20001020 <--
			EP 2000-984583	A3 20001020 <--
			WO 2000-US41360	W 20001020 <--

OTHER SOURCE(S): MARPAT 142:404295

AB Compds. that inhibit the activity of NF- κ B or inhibit the activity of the proteasome or both promote bone formation and hair growth and are thus useful in treating osteoporosis, bone **fracture** or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation; they also stimulate the production of hair follicles and are thus useful in stimulating hair growth, including hair d., in subject where this is desirable.

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:8368 CAPLUS

DOCUMENT NUMBER: 142:107435

TITLE: Inhibitors of proteasomal activity for stimulating **bone growth**

INVENTOR(S): Mundy, Gregory R.; Garrett, I. Ross; Rossini, Jorge Gianni

PATENT ASSIGNEE(S): Osteoscreen Inc., USA

SOURCE: U.S., 26 pp., Cont.-in-part of U.S. Ser. No. 421,545.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 6838436	B1	20050104	US 2000-695807	20001023 <--
US 6462019	B1	20021008	US 1998-113947	19980710 <--
US 6410512	B1	20020625	US 1999-361775	19990727 <--
US 6902721	B1	20050607	US 1999-421545	19991020 <--
US 2002107203	A1	20020808	US 2002-52832	20020115 <--
US 6838252	B2	20050104		
US 2005025734	A1	20050203	US 2004-894189	20040719 <--
US 2005147574	A1	20050707	US 2004-26691	20041230 <--
JP 2006089498	A2	20060406	JP 2005-330878	20051115 <--
AU 2005246961	A1	20060119	AU 2005-246961	20051220 <--
PRIORITY APPLN. INFO.:			US 1998-113947	A2 19980710 <--
			US 1999-361775	A2 19990727 <--
			US 1999-421545	A2 19991020 <--
			JP 2000-558808	A3 19990709 <--
			AU 2001-21183	A3 20001020 <--
			US 2000-695807	A3 20001023 <--
			US 2002-52832	A1 20020115

OTHER SOURCE(S): MARPAT 142:107435

AB The invention discloses compds. that inhibit the activity of the proteasome or the production of proteasomal proteins and promote bone formation and are thus useful in treating osteoporosis, bone **fracture** or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation in subjects where this is desirable.

REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:312010 CAPLUS

DOCUMENT NUMBER: 136:319430

TITLE: Isoprenoid pathway inhibitors for stimulating **bone growth**

INVENTOR(S): Gasper, Shirley R.; West, Robert R.; Martinez, Theresa; Robbins, Kirk G.; McKernan, Patricia A.; Baidur, Nand; Labroo, Virender M.; Mundy, Gregory R.

PATENT ASSIGNEE(S): Zymogenetics Corporation, USA; Osteoscreen, Inc.

SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 96,631.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6376476	B1	20020423	US 2000-488380	20000120 <--
US 6022887	A	20000208	US 1997-989862	19971212 <--
EP 1609469	A2	20051228	EP 2005-21225	19971212 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6080779	A	20000627	US 1998-96957	19980612 <--
US 6410521	B1	20020625	US 2000-541943	20000403 <--
CA 2397659	AA	20010726	CA 2001-2397659	20010119 <--
WO 2001052829	A2	20010726	WO 2001-US1888	20010119 <--
WO 2001052829	A3	20020502		
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1253922	A2	20021106	EP 2001-903155	20010119 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

JP 2003527353 T2 20030916 JP 2001-552877 20010119 <--
 WO 2001074180 A1 20011011 WO 2001-US40421 20010402 <--
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
 CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
 HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
 RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
 VN, YU, ZA, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 US 2001034364 A1 20011025 US 2001-848839 20010503 <--
 US 6642216 B2 20031104
 US 2004106675 A1 20040603 US 2003-652159 20030829 <--
 US 2005272801 A1 20051208 US 2005-167054 20050624 <--
 PRIORITY APPLN. INFO.: US 1996-32893P P 19961213 <--
 US 1997-989862 A2 19971212 <--
 US 1998-96631 B2 19980612 <--
 US 1998-96957 A2 19980612 <--
 EP 1997-954120 A3 19971212 <--
 US 2000-488380 A2 20000120 <--
 US 2000-541943 A 20000403 <--
 WO 2001-US1888 W 20010119
 US 2001-848839 A1 20010503
 US 2003-652159 A1 20030829

OTHER SOURCE(S): MARPAT 136:319430

AB Various embodiments of statin compds. are shown to enhance the formation of bone and are thus useful in treating osteoporosis, bone **fracture** or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation. Studies are reported on high-throughput screening of and effects of statins and **bisphosphonates** on in vivo **bone growth**, bone resorption and **fracture** repair.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:300537 CAPLUS

DOCUMENT NUMBER: 134:331618

TITLE: Inhibitors of proteasomal activity for stimulating bone and hair growth

INVENTOR(S): Mundy, Gregory R.; Garrett, Ross I.; Rossini, G.

PATENT ASSIGNEE(S): Osteoscreen, Inc., USA

SOURCE: PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028579	A2	20010426	WO 2000-US41360	20001020 <--
WO 2001028579	A3	20010920		
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6902721	B1	20050607	US 1999-421545	19991020 <--
US 6884769	B1	20050426	US 2000-558973	20000425 <--
CA 2385958	AA	20010426	CA 2000-2385958	20001020 <--
AU 2001021183	A5	20010430	AU 2001-21183	20001020 <--
EP 1221962	A2	20020717	EP 2000-984583	20001020 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI, CY

JP 2003528039	T2	20030924	JP 2001-531407	20001020 <--
AU 2005246961	A1	20060119	AU 2005-246961	20051220 <--
PRIORITY APPLN. INFO.:			US 1999-421545	A 19991020 <--
			US 2000-558973	A 20000425 <--
			US 1998-113947	A2 19980710 <--
			US 1999-361775	A2 19990727 <--
			AU 2001-21183	A3 20001020 <--
			WO 2000-US41360	W 20001020 <--

OTHER SOURCE(S): MARPAT 134:331618

AB Compds. that inhibit the activity of NF- κ B or inhibit the activity of the proteasome or both promote bone formation and hair growth and are thus useful in treating osteoporosis, bone **fracture** or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation; they also stimulate the production of hair follicles and are thus useful in stimulating hair growth, including hair d., in subject where this is desirable. N-carbobenzoyl-Ile-Glu-(OtBu)Ala-Leu-CHO (PSI) in 50% propylene glycol, 10% DMSO, and 40% water was injected daily for 5 days (1mg/kg body weight/day) into the s.c. tissue of mice and the tissue was examined histol. 16 days later. The number of hair follicles increased and the downward extension of these hair follicles into the dermal tissue was noted, which are hallmarks of anagen. There was an obvious increase in size of the follicle diameter and the root sheath diameter

L6 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:152493 CAPLUS

DOCUMENT NUMBER: 134:173066

TITLE: **Bisphosphonates** for treating **fractures**

INVENTOR(S): Little, David G.

PATENT ASSIGNEE(S): The Royal Alexandra Hospital for Children, Australia

SOURCE: PCT Int. Appl., 53 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001013922	A1	20010301	WO 2000-AU982	20000817 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2381302	AA	20010301	CA 2000-2381302	20000817 <--
BR 2000013416	A	20020430	BR 2000-13416	20000817 <--
EP 1214079	A1	20020619	EP 2000-952791	20000817 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507426	T2	20030225	JP 2001-518059	20000817 <--
NZ 517538	A	20030725	NZ 2000-517538	20000817 <--
AU 781068	B2	20050505	AU 2000-65488	20000817 <--
NO 2002000784	A	20020218	NO 2002-784	20020218 <--
ZA 2002002160	A	20030617	ZA 2002-2160	20020315 <--
PRIORITY APPLN. INFO.:			AU 1999-2325	A 19990819 <--

AB **Bisphosphonates** , e.g. zoledronate and pamidronate, are disclosed for promoting **bone growth** and for the treatment of bone **fractures**.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:650814 CAPLUS

DOCUMENT NUMBER: 133:344701

TITLE: Effects of growth hormone on bone and muscle

AUTHOR(S): Lissett, C. A.; Shalet, S. M.

CORPORATE SOURCE: Department of Endocrinology, Christie Hospital, Manchester, UK

SOURCE: Growth Hormone & IGF Research (2000), 10(Suppl. B), 95-101

CODEN: GHIRF9; ISSN: 1096-6374

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 43 refs. The decade since the initial availability of recombinant growth hormone (GH) has seen an increase in the authors' understanding of the effects of GH on muscle and bone. Adult GH deficiency (GHD) is associated with osteopenia, the severity of which is related to three factors: the timing, age of onset and severity of GHD. Epidemiol. data suggest that this osteopenia is associated with an increased risk of **fracture**. The impact of GH replacement therapy on bone mineral d. (BMD) appears to be related to a large number of interrelated factors, including the dose and duration of therapy, timing of onset of GHD, skeletal site, degree of osteopenia at baseline, and age and gender of the patient. Overall, the effect of GH replacement on BMD in the majority of patients is beneficial. As yet, however, no data are available that demonstrate a reduction in **fracture** rate following GH therapy. In comparison with normal individuals, GH-deficient individuals have reduced lean body mass and muscle strength, both of which increase within 12 mo of GH therapy. Therefore, the effects of GH replacement on muscle and bone in GH-deficient individuals are significant and beneficial, although the longer-term effects of GH replacement in terms of reducing the number of **fractures** and prevention of frailty in old age are not yet established. The effects of GH on bone and muscle in GH-replete individuals have been studied less fully. While GH therapy modulates markers of bone resorption and formation, its effects in patients with idiopathic osteoporosis are disappointing, with estrogen therapy or **bisphosphonates** proving to be more effective in post-menopausal women. To date, however, there have been no GH treatment trials of adequate duration (longer than 18 mo), and it remains possible that longer-term trials may demonstrate more profound effects. The effects of GH therapy on muscle have been examined in normal elderly individuals. Generally, the doses used have been supraphysiol. and associated with an unacceptable incidence of side-effects. GH therapy has resulted in an increase in lean body mass, but functional ability and strength have not improved in the majority of studies. Thus, clear-cut beneficial effects of GH on muscle and bone in GH-replete individuals have not been demonstrated. It seems unlikely that normal elderly individuals will benefit significantly from GH therapy, but frail individuals or those with musculoskeletal or neuromuscular pathol. are potential candidates for study.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:433348 CAPLUS

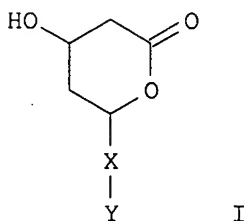
DOCUMENT NUMBER: 133:53725

TITLE: Compositions and methods for stimulating **bone**

INVENTOR(S): **growth**
 Gasper, Shirley R.; West, Robert R.; Martinez,
 Theresa; Robbins, Kirk G.; McKernan, Patricia A.;
 Baindur, Nand; Labroo, Virender M.; Mundy, Gregory R.
 PATENT ASSIGNEE(S): Osteoscreen, Inc., USA; Zymogenetics Corporation
 SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 989,862.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 6
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6080779	A	20000627	US 1998-96957	19980612 <--
US 6022887	A	20000208	US 1997-989862	19971212 <--
EP 1609469	A2	20051228	EP 2005-21225	19971212 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6376476	B1	20020423	US 2000-488380	20000120 <--
US 6410521	B1	20020625	US 2000-541943	20000403 <--
US 2005272801	A1	20051208	US 2005-167054	20050624 <--
PRIORITY APPLN. INFO.:			US 1996-32893P	P 19961213 <--
			US 1997-989862	A2 19971212 <--
			EP 1997-954120	A3 19971212 <--
			US 1998-96631	B2 19980612 <--
			US 1998-96957	A2 19980612 <--
			US 2000-488380	A2 20000120 <--
			US 2001-848839	A1 20010503
			US 2003-652159	A1 20030829

OTHER SOURCE(S): MARPAT 133:53725
 GI



AB Compds. of the formulas I or Y-X-CHOHCH₂CHOHCH₂COOR' wherein X in each of formulas represents a substituted or unsubstituted alkylene, alkenylene, or alkynylene linker of 2-6 C; Y represents one or more carbocyclic or heterocyclic rings; when two or more rings are present in Y, they may optionally be fused; and R' represents a cation, H or a substituted or unsubstituted alkyl group of 1-6 C; and the dotted lines represent optional π -bonds, promote bone formation and are thus useful in treating osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation. These compds. can be used in combination with other bone growth-promoting compds. and/or estrogens and/or bisphosphonates for this purpose.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:411024 CAPLUS

DOCUMENT NUMBER: 133:115229
 TITLE: The parathyroid hormone, its fragments and analogues - potent bone-builders for treating osteoporosis
 AUTHOR(S): Whitfield, James; Morley, Paul; Willick, Gordon
 CORPORATE SOURCE: Institute for Biological Sciences, National Research Council of Canada, Ottawa, ON, Can.
 SOURCE: Expert Opinion on Investigational Drugs (2000), 9(6), 1293-1315
 CODEN: EOIDER; ISSN: 1354-3784
 PUBLISHER: Ashley Publications Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review with 159 refs. As populations age a rising number of men and women, but especially women during the first decade after menopause, become victims of a severe, accelerated loss of bone with crippling **fractures** known as osteoporosis. This often results in costly, prolonged hospitalization and perhaps indirectly, death. Osteoporosis in women is caused by the menopausal estrogen decline, which removes several key restraints on the generation, longevity and activity of bone-resorbing osteoclasts. Although there are many antiresorptive drugs on or coming onto the market (calcitonin, **bisphosphonates**, estrogen and SERMS) that can slow or stop further bone loss, there are none that can restore lost bone mech. strength by directly stimulating osteoblast activity and **bone growth**. However, there is a family of potent bone-building peptides, namely the 84 amino acid parathyroid hormone (PTH). Its 31 to 38 amino acid N-terminal fragments are currently in or about to enter clin. trials. The authors can predict that these peptides will be effective therapeutics for osteoporosis especially when supplemented with **bisphosphonates** or SERMs to protect the new bone from osteoclasts. These peptides should also accelerate the healing of **fractures** in persons of all ages and restore lost bone mass and mech. strength to astronauts following their return to earth after long voyages in space.

REFERENCE COUNT: 161 THERE ARE 161 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L6 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:53374 CAPLUS
 DOCUMENT NUMBER: 132:102860
 TITLE: Inhibitors of proteasomal activity for stimulating bone and hair growth
 INVENTOR(S): Mundy, Gregory R.; Garrett, I. Ross; Rossini, G.
 PATENT ASSIGNEE(S): Osteoscreen, USA
 SOURCE: PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 6
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000002548	A2	20000120	WO 1999-US15533	19990709 <--
WO 2000002548	A3	20030417		
W:	AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SD, SG, SI, SK, TR, TT, US, UZ, VN			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6462019	B1	20021008	US 1998-113947	19980710 <--
CA 2337988	AA	20000120	CA 1999-2337988	19990709 <--

AU 9963109	A1	20000201	AU 1999-63109	19990709 <--
AU 771297	B2	20040318		
EP 1096924	A1	20010509	EP 1999-933827	19990709 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003522107	T2	20030722	JP 2000-558808	19990709 <--
JP 2006089498	A2	20060406	JP 2005-330878	20051115 <--
AU 2005246961	A1	20060119	AU 2005-246961	20051220 <--
PRIORITY APPLN. INFO.:			US 1998-113947	A1 19980710 <--
			JP 2000-558808	A3 19990709 <--
			WO 1999-US15533	W 19990709 <--
			AU 2001-21183	A3 20001020 <--

AB Compds. that inhibit the activity of NF- κ B or inhibit the activity of the proteasome or both promote bone formation and hair growth and are thus useful in treating osteoporosis, bone **fracture** or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation. They also stimulate the production of hair follicles and are thus useful in stimulating hair growth, including hair d., in subject where this is desirable.

L6 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:672304 CAPLUS
DOCUMENT NUMBER: 131:295931
TITLE: Treatment of skeletal disorders using leptin or a leptin mimetic
INVENTOR(S): Ke, Hua Zhu; Stepan, Claire Monica; Swick, Andrew Gordon
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 950417	A2	19991020	EP 1999-301084	19990215 <--
EP 950417	A3	20000223		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6352970	B1	20020305	US 1999-253329	19990219 <--
CA 2262269	C	20030715	CA 1999-2262269	19990219 <--
CA 2262269	AA	19990823		
JP 11315030	A2	19991116	JP 1999-43193	19990222 <--
BR 9900775	A	20000328	BR 1999-775	19990222 <--
US 2002019351	A1	20020214	US 2001-965760	20010927 <--
PRIORITY APPLN. INFO.:			US 1998-75491P	P 19980223 <--
			US 1999-253329	A3 19990219 <--

AB This invention relates to methods for treating bone loss in a mammal by administering to the mammal a therapeutically effective amount of leptin or a leptin mimetic. This invention also relates to methods for treating bone **fracture**, enhancing bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction, enhancing long bone extension, enhancing the healing rate of a bone graft, enhancing prosthetic growth and inducing vertebral synostosis by administering a therapeutically effective amount of leptin or a leptin mimetic. This invention further relates to methods and compns. comprising leptin or a leptin mimetic and estrogen, a selective estrogen receptor modulator or a **bisphosphonate** for treating the above-recited diseases and conditions. Pharmaceutical compns. and kits containing the compds. of the invention are also claimed.

L6 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:742750 CAPLUS
DOCUMENT NUMBER: 126:14572
TITLE: Current bone mineral density data on
bisphosphonates in postmenopausal osteoporosis
AUTHOR(S): McClung, M. R.
CORPORATE SOURCE: Oregon Osteoporosis Center, Portland, OR, 97213, USA
SOURCE: Bone (New York) (1996), 19(5, Suppl.),
195S-198S
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Osteoporosis is a disorder of skeletal fragility characterized by an imbalance in bone turnover such that bone resorption exceeds bone formation. Accelerated bone resorption is the principal physiologic derangement responsible for both postmenopausal and age-related bone loss. Furthermore, increased bone turnover is itself a risk factor for **fracture**, independent of bone mineral density. Thus, there is a strong rationale for the use of potent antiresorptive drugs for the treatment of postmenopausal osteoporosis. **Bisphosphonates** are a class of drugs that inhibit osteoclast activity and bone resorption. Recent studies with etidronate, pamidronate, and alendronate demonstrate the ability of these drugs to suppress bone turnover and to preserve or increase bone mass. In large studies with alendronate, in long-term studies with clodronate, and in patients at high **fracture** risk treated with etidronate, decreased **fracture** occurrence is observed. Except for upper gastrointestinal intolerance with aminobisphosphonates, these drugs are very well tolerated. **Bisphosphonates** are promising alternatives to estrogen for the treatment of patients with decreased bone mass and, particularly, those with severe osteoporosis. Further studies are needed to define the optimal long-term dosing regimen and to establish whether more potent members of this drug class are more effective or can be administered by different routes. The effectiveness of **bisphosphonates** in combination with estrogen or **bone growth** stimulators also requires evaluation, and the extended long-term safety of these drugs must be determined.

L6 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:400053 CAPLUS
DOCUMENT NUMBER: 115:53
TITLE: Pamidronate. A review of its pharmacological properties and therapeutic efficacy in resorptive bone disease
AUTHOR(S): Fitton, Andrew; McTavish, Donna
CORPORATE SOURCE: Adis Drug Inf. Serv., Auckland, N. Z.
SOURCE: Drugs (1991), 41(2), 289-318
CODEN: DRUGAY; ISSN: 0012-6667
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 148 refs. Pamidronate [aminohydroxypropylidene diphosphonate disodium (APD), disodium pamidronate] is an orally and i.v. active amino-substituted **bisphosphonate** which produces potent and specific inhibition of bone resorption at doses devoid of any significant detrimental effect on **bone growth** and mineralization. Clinical trials indicate that pamidronate is effective in a variety of conditions characterized by pathologically enhanced bone turnover, including Paget's disease, hypercalcemia of malignancy, osteolytic bone metastasis, steroid-induced osteoporosis and idiopathic osteoporosis. Pamidronate is highly effective in restoring normocalcemia in patients with hypercalcemia of malignancy associated with bone metastases but, in common with other **bisphosphonates**, is marginally less effective against humoral hypercalcemia of malignancy. Comparative studies in this area have

suggested that, at therapeutic doses, pamidronate has a more pronounced calcium-lowering action than etidronate (etidronic acid) and clodronate (clodronic acid) and provides a longer period of normocalcemic remission. In Paget's disease arrest and, in some patients, reversal of the progression of osteolytic lesions by pamidronate is associated with a sustained reduction in bone pain, improved mobility and a possible reduced risk of bone **fracture**. In patients with osteolytic bone metastasis pamidronate reduces skeletal morbidity and slows the progression of metastatic bone destruction. Long term use of low-dose pamidronate in conjunction with conventional antiosteoporotic therapy may halt bone loss in steroid-induced and idiopathic osteoporosis. Pamidronate appears to represent a valuable addition to the drugs currently available for the treatment of symptomatic Paget's disease and cancer-associated hypercalcemia, and shows promise in the treatment of osteolytic bone metastasis and osteoporosis.

L6 ANSWER 13 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97339201 EMBASE
DOCUMENT NUMBER: 1997339201
TITLE: Osteoporosis in men.
AUTHOR: Seeman E.
CORPORATE SOURCE: Dr. E. Seeman, Associate Department Endocrinology, Austin Repatriation Medical Centre, University of Melbourne, Heidelberg 3084, Melbourne, Australia
SOURCE: Bailliere's Clinical Rheumatology, (1997) Vol. 11, No. 3, pp. 613-628. .
Refs: 31
ISSN: 0950-3579 CODEN: BCRHEZ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 020 Gerontology and Geriatrics
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Nov 1997
Last Updated on STN: 20 Nov 1997

AB Hip **fractures** in men account for one third of all hip **fractures** and have a higher mortality than in women. The public health burden will increase as the increase in the numbers of elderly men in the community increases. In addition, the age-specific incidence of hip **fractures** may be increasing in some, but not all, countries. Vertebral **fractures** may be a public health problem as recent studies suggest that the prevalence in the community is 20-30%, similar to that reported in women. Forearm **fractures** should probably not be regarded as a public health problem. Peak bone mass is higher in men than women because men have bigger bones. Peak bone mineral density is the same. The amount of trabecular bone lost at the spine and iliac crest during ageing is similar in men and women. Cortical bone loss is less in men because endocortical resorption is less and periosteal formation is greater. Bone loss accelerates in elderly men because endocortical resorption and increasing cortical porosity increase the surface available for resorption. Bone fragility is less in men than women because: (a) the cross-sectional surface of the bone is larger; (b) trabecular bone loss is less as a percentage of the higher peak bone mass; (c) trabecular bone loss occurs by thinning rather than perforation; and (d) periosteal appositional growth compensates for endocortical resorption by maintaining the bending strength of bone. Reduced BMD in men with **fractures** may be due to reduced peak bone size and mass, and bone loss. Bone loss occurs by reduced bone formation. Whether men with **fractures** have increased bone fragility due to reduced periosteal appositional growth during ageing is unknown. The age-related decline in testosterone, adrenal androgens, growth hormone, and insulin-like growth factor 1 may contribute to reduced bone formation and bone loss. Men with vertebral

fractures often have hypogonadism or illnesses with few clinical features that should be considered with a high index of suspicion (alcoholism, myeloma, malabsorption, primary hyperparathyroidism, haemochromatosis, Cushing's disease). Secondary hyperparathyroidism may contribute to bone loss by activating bone turnover and so increasing the number of bone remodelling units with impaired bone formation in each. There is no proven treatment for osteoporosis in men because there have been no trials using anti-**fracture** efficacy as an end point. Testosterone replacement should be considered in men with proven hypogonadism and vitamin D deficiency should be corrected if present. Calcium supplements and **bisphosphonates** are reasonable options given the lack of information.

L6 ANSWER 14 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97268403 EMBASE
DOCUMENT NUMBER: 1997268403
TITLE: Recent progress in diagnosis and treatment of osteogenesis imperfecta.
AUTHOR: Moriwake T.; Seino Y.
CORPORATE SOURCE: Dr. T. Moriwake, Department of Pediatrics, Okayama University Medical School, 2-5-1 Shikatacho, Okayama 700, Japan
SOURCE: Acta Paediatrica Japonica (Overseas Edition), (1997) Vol. 39, No. 4, pp. 521-527. .
Refs: 46
ISSN: 0374-5600 CODEN: APDJBE
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
022 Human Genetics
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 1997
Last Updated on STN: 2 Oct 1997

AB Osteogenesis imperfecta (OI) is an inheritable disorder characterized by bone fragility with various symptoms of connective tissue disorders. OI is commonly classified by Sillence's classification into four types according to the clinical features. The cardinal symptom is pathologic **fracture**, which is often recognized before birth, is frequent during infancy and childhood, then decreases at puberty. Bone mineral density is markedly decreased in OI, especially of the lumbar spine. Bone deformities are frequently observed in the long bones of the extremities, and spinal deformities and compression **fractures** are also common. Growth retardation is extremely severe, especially in type III. Calcitonin has been the most common therapy for OI. Recently, **bisphosphonates** have been found to be potent drugs that increase bone mass in OI patients. To prevent further **fracture** or bone deformity, appropriate orthopedic managements, including intramedullary rodding, are critically important. Growth hormone is effective in stimulating **bone growth** during childhood. The pathogenesis of OI is quantitative or qualitative abnormalities of type I collagen. Tire clinical features of each type usually correspond to the type of mutation. Several possibilities for gene therapy have been proposed.

L6 ANSWER 15 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97258163 EMBASE
DOCUMENT NUMBER: 1997258163
TITLE: Long-term effects of **bisphosphonates** on the

growing skeleton: Studies of young patients with severe osteoporosis.

AUTHOR: Brumsen C.; Hamdy N.A.T.; Papapoulos S.E.

CORPORATE SOURCE: Dr. S.E. Papapoulos, Department of Endocrinology, Bldg 1, University Hospital, Albinusdreef 2, 2333 AA Leiden, Netherlands

SOURCE: Medicine, (1997) Vol. 76, No. 4, pp. 266-283. .
 Refs: 109
 ISSN: 0025-7974 CODEN: MEDIAV

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 006 Internal Medicine
 007 Pediatrics and Pediatric Surgery
 033 Orthopedic Surgery
 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 18 Sep 1997
 Last Updated on STN: 18 Sep 1997

AB Osteoporosis in children and adolescents is relatively uncommon and usually secondary to identifiable causal factors. There are no generally accepted therapies for patients with no treatable underlying cause of disease. Any treatment of young patients with bone-acting compounds should be not only effective but also devoid of adverse effects on **bone growth** and remodeling. For many years we have been studying the effects of **bisphosphonates**-an effective treatment of postmenopausal osteoporosis-on the growing skeleton. We review here our experience in the treatment of young patients with osteoporosis with special emphasis on issues of skeletal safety and effectiveness, and we discuss the available literature data. We studied 12 patients aged between 10.7 and 17.2 years with symptomatic osteoporosis and multiple **fractures** treated with the **bisphosphonates** pamidronate or olpadronate for periods between 2 and 8 years continuously. Linear growth continued normally on treatment; there was even a catch-up growth in prepubertal patients, and there was no excessive suppression of bone remodeling, assessed biochemically. Bone biopsies obtained at various stages during treatment showed bone of normal lamellar structure without mineralization defects. There was an increase in calcium balance, already evident within 10 days, the level of which was maintained for at least 3 years of treatment. This was associated with progressive increases in bone mineral density along a different slope from that of healthy peers as well as correction of vertebral deformities on X-rays in patients given **bisphosphonates** before puberty. Treatment was well tolerated and clinical improvement was remarkable. Our studies, supported by literature data, strongly suggest that **bisphosphonate** therapy can be beneficial to young patients with osteoporosis for whom no other options are currently available, and justify planning controlled studies in more common conditions for which no treatment is currently available, such as osteogenesis imperfecta.

L6 ANSWER 16 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 96360275 EMBASE

DOCUMENT NUMBER: 1996360275

TITLE: Current bone mineral density data on **bisphosphonates** in postmenopausal osteoporosis.

AUTHOR: McClung M.R.

CORPORATE SOURCE: Oregon Osteoporosis Center, 5050 NE Hoyt Street, Portland, OR 97213, United States

SOURCE: Bone, (1996) Vol. 19, No. 5 SUPPL., pp. 195S-198S. .
 ISSN: 8756-3282 CODEN: BONEDL

PUBLISHER IDENT.: S 8756-3282(96)00264-5

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 003 Endocrinology
030 Pharmacology
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 23 Dec 1996

Last Updated on STN: 23 Dec 1996

AB Osteoporosis is a disorder of skeletal fragility characterized by an imbalance in bone turnover such that bone resorption exceeds bone formation. Accelerated bone resorption is the principal physiological derangement responsible for both postmenopausal and age-related bone loss. Furthermore, increased bone turnover is itself a risk factor for **fracture**, independent of bone mineral density. Thus, there is a strong rationale for the use of potent antiresorptive drugs for the treatment of postmenopausal osteoporosis. **Bisphosphonates** are a class of drugs that inhibit osteoclast activity and bone resorption. Recent studies with etidronate, pamidronate, and alendronate demonstrate the ability of these drugs to suppress bone turnover and to preserve or increase bone mass. In large studies with alendronate, in long-term studies with clodronate, and in patients at high **fracture** risk treated with etidronate, decreased **fracture** occurrence is observed. Except for upper gastrointestinal intolerance with aminobisphosphonates, these drugs are very well tolerated. **Bisphosphonates** are promising alternatives to estrogen for the treatment of patients with decreased bone mass and, particularly, those with severe osteoporosis. Further studies are needed to define the optimal long-term dosing regimen and to establish whether more potent members of this drug class are more effective or can be administered by different routes. The effectiveness of **bisphosphonates** in combination with estrogen or **bone growth** stimulators also requires evaluation, and the extended long-term safety of these drugs must be determined.

L6 ANSWER 17 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 95329402 EMBASE

DOCUMENT NUMBER: 1995329402

TITLE: Small bone-building fragments of parathyroid hormone: New therapeutic agents for osteoporosis.

AUTHOR: Whitfield J.F.; Morley P.

CORPORATE SOURCE: Institute of Biological Sciences, National Research Council of Canada, Ottawa, Ont. K1A 0R6, Canada

SOURCE: Trends in Pharmacological Sciences, (1995) Vol. 16, No. 11, pp. 382-386. .

ISSN: 0165-6147 CODEN: TPHSDY

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 002 Physiology
003 Endocrinology
005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
033 Orthopedic Surgery
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 5 Dec 1995

Last Updated on STN: 5 Dec 1995

AB The brittle, **fracture**-prone bones of an osteoporotic postmenopausal woman are the products of an excessive uncompensated resorption of trabecular bone by osteoclasts. Osteoporosis is currently treated with the osteoclast suppressors calcitonin,

bisphosphonates, or oestrogen, which stop further bone resorption without stimulating new **bone growth**. Here, James Whitfield and Paul Morley review the growing evidence that small adenylate cyclase-stimulating fragments of the parathyroid hormone are promising therapeutic agents for osteoporosis that potently stimulate osteoblasts to make mechanically strong or supranormally strong bone.

L6 ANSWER 18 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 94275520 EMBASE
DOCUMENT NUMBER: 1994275520
TITLE: Aminohydroxy propylidene **bisphosphonate** (APD) treatment improves the clinical skeletal manifestations of Gaucher's disease.
AUTHOR: Samuel R.; Katz K.; Papapoulos S.E.; Yosipovitch Z.; Zaizov R.; Liberman U.A.
CORPORATE SOURCE: Unit of Metabolic Diseases, Beilinson Medical Center, Petah Tiqva 49 100, Israel
SOURCE: Pediatrics, (1994) Vol. 94, No. 3, pp. 385-389. .
ISSN: 0031-4005 CODEN: PEDIAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective. To evaluate the long-term effects and safety of aminohydroxy propylidene **bisphosphonate** (APD) treatment on the frequency and severity of the clinical skeletal manifestations of Gaucher's disease. Methodology. Five adolescents who suffered from recurrent bone crisis episodes and atraumatic bone **fractures** due to Gaucher's disease were treated with APD for 14 to 83 months. Results. During the 6 years before treatment, the patients suffered from 6 to 17 bone crisis episodes, or 1 to 2.8 episodes per patient per year. Three patients were free from bone crisis episodes during 14 to 32 months of APD treatment, while two patients had two such episodes during 60 and 83 months of APD treatment (these represent a decrease in bone crisis episodes from 1 and 2.8 per year to 0.4 and 0.3 per year, respectively). Although four patients suffered from 1 to 3 atraumatic bone **fractures** during the 6 years preceding treatment (a total of 10 **fractures**), only one patient sustained a **fracture** on APD treatment (total of 219 months of treatment). Using APD was not associated with clinical side effects, biochemical aberrations, significant changes in liver and kidney function, or changes in serum levels of the hormones regulating mineral metabolism. In all patients, a band-like metaphyseal sclerosis appeared on radiography of the long bone. However, APD did not interfere with **bone growth**. Conclusions. The marked clinical improvement in the clinical skeletal manifestations of Gaucher's disease and the absence of toxic side effects in adolescent patients treated with APD support previous findings in three adult patients on the efficacy of APD and indicate possibilities for its use in inducing prolonged remissions in affected patients.

L6 ANSWER 19 OF 19 MEDLINE on STN
ACCESSION NUMBER: 97119447 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8960270
TITLE: The effects of pamidronate on mechanical properties, growth and structural changes in rat bones.
AUTHOR: Kaczmarczyk-Sedlak I
CORPORATE SOURCE: Department of Pharmacology, Silesian School of Medicine, Sosnowiec, Poland.

SOURCE: Acta poloniae pharmaceutica, (1995 Nov-Dec) Vol.
52, No. 6, pp. 509-13.
Journal code: 2985167R. ISSN: 0001-6837.

PUB. COUNTRY: Poland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199701

ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970124

AB Although a number of properties of **bisphosphonates** have been recognized which influence the metabolic process in bones, particularly those concerning the remodelling processes, the influence of this new group of drugs on the mechanical properties of bones remains an open issue. In order to clarify this problem, the present study concentrated on the influence of a new generation **bisphosphonate**, i.e. pamidronate upon the mechanical properties, growth, and morphological changes in the femoral and tibial bones in rats. The experiments carried out concerned pamidronate administration to male Wistar rats in doses of 3 mg/kg of body mass subcutaneously, for the period of 3 or 6 weeks. The total changes in the osseous tissue after pamindronate administration indicate the drug to foster the development of osteopetrosis in rats, the prominent sings of the disease being mainly deformations of epiphysis, decreased **bone growth**, increased thickness of epiphysial cartilage and bone trabeculae, as well as lowered resistance to **fractures** and decreased susceptibility to deformations.

=> d L11 1-13 ibib abs

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:368351 CAPLUS

DOCUMENT NUMBER: 136:366118

TITLE: Non-isotopic detection of osteoblastic activity in vivo using modified bisphosphonates

INVENTOR(S): Frangioni, John V.

PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA

SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002038190	A2	20020516	WO 2001-US51312	20011029 <--
WO 2002038190	A3	20020829		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2002036683	A5	20020521	AU 2002-36683	20011029 <--
EP 1341557	A2	20030910	EP 2001-986230	20011029 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2004028611	A1	20040212	US 2003-424572	20030425 <--
US 6869593	B2	20050322		

US 2006002857 A1 20060105 US 2004-979786 20041102 <--
 PRIORITY APPLN. INFO.: US 2000-244020P P 20001027 <--
 WO 2001-US51312 W 20011029
 US 2003-424572 A1 20030425

OTHER SOURCE(S): MARPAT 136:366118

AB The present invention is directed to a non-isotopic methods for the in vitro and in vivo detection of hydroxyapatite-pos. cells and structures. The NHS ester of the near-IR fluorophore IRDye78 was conjugated with pamidronate disodium to make Pam78. Pam78 was used in near-IR fluorescence imaging of hydroxyapatite in hairless mice. As early as 15 min post-injection, Pam78 uptake in the spine, ribs, paws, and knees could be detected above background, and by three hours, most bony structures were visible.

L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:122767 CAPLUS

DOCUMENT NUMBER: 136:178014

TITLE: Aryl-substituted 1,1-diphosphonates for stimulating bone formation

INVENTOR(S): Niesor, Eric J.; Guyon-Gellin, Yves; Bentzen, Craig L.; Nguyen, Lan Mong; Phan, Hieu Trung

PATENT ASSIGNEE(S): Symphar S.A., Switz.

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011704	A2	20020214	WO 2001-EP8676	20010727 <--
WO 2002011704	A3	20020718		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2417606	AA	20020214	CA 2001-2417606	20010727 <--
AU 2002012117	A5	20020218	AU 2002-12117	20010727 <--
EP 1326618	A2	20030716	EP 2001-980218	20010727 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2004505908	T2	20040226	JP 2002-517041	20010727 <--
PRIORITY APPLN. INFO.:			GB 2000-19272	A 20000804 <--
			WO 2001-EP8676	W 20010727

OTHER SOURCE(S): MARPAT 136:178014

AB The invention provides the use of an aryl-substituted 1,1-diphosphonate for the manufacture of a medicament for stimulating bone formation. The aryl-substituted 1,1-diphosphonates of the invention are ALC(PO3R1R2)(PO3R3R4)(B)t where [A = Q1-Q3; X0 = H, C1-4 alkyl; X1-X3 = H, C1-8 (un)branched alkyl or alkoxy; X4 = H, C1-8 (un)branched alkyl, (un)substituted benzyl; X5 = H, C1-8 (un)branched alkyl; X6 = H, C1-4 alkyl; q = 0, 1; R1-R4 = H, C1-8 (un)branched or cyclic alkyl, or R1, R2 and R3 and R4 may form C2-8 alkylidenedioxy ring; L = CH=CH-CH2, (CH2)n, O(CH2)n, S, SO2, S(CH2)n, SO2(CH2)n (n = 1-7), or together with B, L is (CH=CH)k(CH2)dCH= (k = 0, 1); d = 0-4; B = H, C1-4 alkyl; t = 0, 1; with provisos]. Synthesis of selected compds. is described.

L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:747981 CAPLUS
 DOCUMENT NUMBER: 135:283230
 TITLE: Identifying geranylgeranyl diphosphate synthase inhibitors and their use for inhibiting bone resorption
 INVENTOR(S): Rodan, Gideon A.; Reszka, Alfred A.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 30 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001075081	A1	20011011	WO 2001-US9946	20010327 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002004218	A1	20020110	US 2001-817432	20010326 <--
CA 2403735	AA	20011011	CA 2001-2403735	20010327 <--
EP 1280891	A1	20030205	EP 2001-926463	20010327 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003529365	T2	20031007	JP 2001-572955	20010327 <--
PRIORITY APPLN. INFO.: US 2000-194263P P 20000331 <-- WO 2001-US9946 W 20010327				

OTHER SOURCE(S): MARPAT 135:283230
 AB The present invention relates to methods for identifying compds. useful as inhibitors of geranylgeranyl diphosphate synthase. More particularly, the compds. so identified are useful for inhibiting bone resorption. The present invention also relates to methods for inhibiting bone resorption in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of a geranylgeranyl diphosphate synthase inhibitor.
 REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:152493 CAPLUS
 DOCUMENT NUMBER: 134:173066
 TITLE: Bisphosphonates for treating **fractures**
 INVENTOR(S): Little, David G.
 PATENT ASSIGNEE(S): The Royal Alexandra Hospital for Children, Australia
 SOURCE: PCT Int. Appl., 53 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001013922	A1	20010301	WO 2000-AU982	20000817 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2381302	AA	20010301	CA 2000-2381302	20000817 <--
BR 2000013416	A	20020430	BR 2000-13416	20000817 <--
EP 1214079	A1	20020619	EP 2000-952791	20000817 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507426	T2	20030225	JP 2001-518059	20000817 <--
NZ 517538	A	20030725	NZ 2000-517538	20000817 <--
AU 781068	B2	20050505	AU 2000-65488	20000817 <--
NO 2002000784	A	20020218	NO 2002-784	20020218 <--
ZA 2002002160	A	20030617	ZA 2002-2160	20020315 <--
PRIORITY APPLN. INFO.:			AU 1999-2325	A 19990819 <--
			WO 2000-AU982	W 20000817 <--

AB Bisphosphonates , e.g. **zoledronate** and pamidronate, are
disclosed for promoting bone growth and for the treatment of bone
fractures.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:891342 CAPLUS

DOCUMENT NUMBER: 135:55654

TITLE: Changes in cross-sectional geometry of the distal
femoral metaphysis associated with inflammatory
arthritis are reduced by a bisphosphonate (
zoledronate)

AUTHOR(S): Pysklywec, Michael W.; Moran, Erica L.; Bogoch, Earl
R.

CORPORATE SOURCE: Orthopaedic Research Laboratory, University of
Toronto, Toronto, ON, M4Y 1J3, Can.

SOURCE: Journal of Orthopaedic Research (2000),
18(5), 734-738
CODEN: JOREDR; ISSN: 0736-0266

PUBLISHER: Journal of Bone and Joint Surgery, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An increased risk of **fracture** is a feature of rheumatoid
arthritis and of animal models of inflammatory arthritis. The authors
examined geometrical changes in the metaphyseal cortex of the distal femur
in an animal model of inflammatory arthritis. Addnl., the authors examined
the effect of a bisphosphonate in preventing these changes. 5 Groups of
rabbits were studied: normal controls, those with inflammatory arthritis,
and 3 groups with arthritis treated with bisphosphonate. To determine
geometrical properties, image anal. was performed on digitized cross
sections of the femoral metaphyseal cortices. The results demonstrated
that the posterior cortical wall was less thick in rabbits with arthritis
than in normal rabbits and in the rabbits in the 3 bisphosphonate
treatment groups. Moment of inertia about the lateral-medial axis was
reduced in rabbits with arthritis compared with normal rabbits.
Cross-sectional area was not different between groups. The changes
suggest a mechanism of weakening of bone in arthritis; when the results
are coupled with results of previous porosity studies, severe directional
weakness is apparent. Bisphosphonate was effective in preserving bone
integrity in inflammatory arthritis.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:628299 CAPLUS

DOCUMENT NUMBER: 133:203006
 TITLE: Methods for identifying compounds useful for inhibiting farnesyl diphosphate synthase for use in inhibiting bone resorption and in pharmaceuticals
 INVENTOR(S): Bergstrom, James D.; Reszka, Alfred A.; Rodan, Gideon A.
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 32 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052198	A1	20000908	WO 2000-US5338	20000301 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2362985	AA	20000908	CA 2000-2362985	20000301 <--
EP 1159447	A1	20011205	EP 2000-912106	20000301 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537819	T2	20021112	JP 2000-602808	20000301 <--
AU 775239	B2	20040722	AU 2000-33890	20000301 <--
PRIORITY APPLN. INFO.:			US 1999-122997P	P 19990305 <--
			WO 2000-US5338	W 20000301 <--

OTHER SOURCE(S): MARPAT 133:203006
 AB The present invention relates to methods for identifying compds. useful as inhibitors of farnesyl diphosphate synthase. More particularly, the compds. so identified are useful for inhibiting bone resorption. The present invention also relates to methods for inhibiting bone resorption in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of a farnesyl diphosphate synthase inhibitor.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:444528 CAPLUS
 DOCUMENT NUMBER: 133:83613
 TITLE: Bisphosphonates and breast carcinoma: present and future
 AUTHOR(S): Lipton, Allan
 CORPORATE SOURCE: Division of Hematology/Oncology, Milton S. Hershey Medical Center, Hershey, PA, 17033, USA
 SOURCE: Cancer (New York) (2000), 88(12, Suppl.), 3033-3037
 CODEN: CANCAR; ISSN: 0008-543X
 PUBLISHER: John Wiley & Sons, Inc.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with 24 refs. BACKGROUND: Bisphosphonates are analogs of endogenous pyrophosphates in which a carbon atom replaces the central atom of oxygen. Bisphosphonates are potent inhibitors of osteoclastic bone resorption and are effective in decreasing the incidence of skeletal complications in breast carcinoma patients with osteolytic bone metastases. METHODS: Zoledronate is a new, potent

third-generation bisphosphonate that is 500-1000 times more potent than pamidronate. A Phase II clin. trial of 0.4, 2.0, or 4.0 mg of **zoledronate** as a 5-min infusion or 90 mg of pamidronate as a 2-h infusion recently was completed. In addition, osteoprotegerin (OPG) recently has been identified as a novel, naturally occurring protein that inhibits osteoclast formation. RESULTS: A 5-min infusion of 2.0 or 4.0 mg of **zoledronate** is at least as effective as 90 mg of pamidronate in preventing skeletal complications. OPG currently is entering Phase I clin. trials. Finally, tumor cells staining strongly for matrix metalloproteinases are observed in osteolytic pathol. bone **fractures** secondary to metastatic carcinoma. In many of these lesions frequent tumor cells are observed and osteoclasts are rare. CONCLUSIONS: Bisphosphonate treatment can decrease skeletal events in patients with breast carcinoma that is metastatic to bone. Current trials to improve results further are employing more potent bisphosphonates such as **zoledronate** and nonbisphosphate inhibitors of osteoclasts such as OPG. An osteoclast-independent phase of bone destruction also deserves further consideration.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:260002 CAPLUS
DOCUMENT NUMBER: 132:288773
TITLE: Methods for regulating bone formation
INVENTOR(S): Harada, Shun-ichi; Machwate, Mohamed; Rodan, Gideon A.; Rodan, Sevgi B.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021523	A1	20000420	WO 1999-US23755	19991012 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2346036	AA	20000420	CA 1999-2346036	19991012 <--
EP 1121113	A1	20010808	EP 1999-954865	19991012 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002527386	T2	20020827	JP 2000-575499	19991012 <--
PRIORITY APPLN. INFO.:				
			US 1998-104338P	P 19981015 <--
			GB 1998-24574	A 19981109 <--
			WO 1999-US23755	W 19991012 <--

AB The present invention relates to methods for regulating bone formation in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of an inhibitor of apoptosis of cells of osteoblastic lineage.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:691780 CAPLUS

DOCUMENT NUMBER: 130:231665
TITLE: The role of bisphosphonates in the treatment of
painful metastatic bone disease: a review of phase III
trials
AUTHOR(S): Fulfaro, F.; Casuccio, A.; Ticozzi, C.; Ripamonti, C.
CORPORATE SOURCE: Pain Therapy and Palliative Care Division, National
Cancer Institute, Milan, 20133, Italy
SOURCE: Pain (1998), 78(3), 157-169
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with many refs. Metastatic bone disease is a frequent cause of morbidity in advanced cancer patients with a subsequent high incidence of skeletal complications (**fractures**, hypercalcemia, spinal cord compression) and severe pain. The osteolytic process is mainly characterized by an osteoclastic activity of bone resorption and inflammatory activity provoked by various cytokines and prostaglandins. Bisphosphonates represent a new class of drugs with inhibitory activity on bone resorption and on inflammatory processes which revealed themselves to be efficacious in a series of clin. conditions such as tumor-induced hypercalcemia, Paget's disease, osteoporosis and metastatic bone disease. The aim of this review of the literature is to show the analgesic efficacy of the different bisphosphonates in phase III studies carried out on patients with metastatic bone disease. Medline and Cancerlit database from Jan. 1984 to Feb. 1998 have been considered. From the anal. of the published studies it appears that bisphosphonates and, in particular, i.v. Disodium Pamidronate, are not only able to slow down the progression of the disease and to reduce the onset of skeletal complications but also have an analgesic effect and the possibility of improving the quality of life, above all in patients with osteolytic metastases due to breast cancer and multiple myeloma. Bisphosphonates represent a further valid therapy to add to an already consolidated list of therapies such as radio, chemo and endocrine therapy, analgesic drugs, orthopedic and 'physiatric in the pain management of patients with bone metastases. These drugs meet with the patients' compliance, are well-tolerated as well as having a good cost/efficacy profile. It still remains to be seen if the newer and more potent bisphosphonates such as Ibandronate and **Zoledronate** can be administered differently from the i.v. route such as by mouth or by patch which are readily accepted by the patient and, moreover, if these more potent drugs are able to prevent or delay the onset and/or the progression of bone metastases.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001002014 EMBASE
TITLE: Bisphosphonates - Clinical applications in osteoporosis.
AUTHOR: Ebeling P.R.
CORPORATE SOURCE: Prof. P.R. Ebeling, Dept. of Diabetes and Endocrinology,
Royal Melbourne Hospital, Melbourne, Vic., Australia.
p.ebeling@medicine.unimelb.edu.au
SOURCE: Australian Prescriber, (2000) Vol. 23, No. 6, pp. 133-136.
Refs: 14
ISSN: 0312-8008 CODEN: AUPRFZ
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
010 Obstetrics and Gynecology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 11 Jan 2001

Last Updated on STN: 11 Jan 2001

AB Bisphosphonates are effective treatments for the prevention and treatment of osteoporosis. In particular, alendronate and risedronate increase bone mineral density and reduce the spinal **fracture** rate to approximately 50% of that in controls, within one year. A less potent, 'first generation' bisphosphonate, etidronate, has also shown anti-**fracture** efficacy. Alendronate also reduces **fracture** rates at the hip and other non-vertebral sites in osteoporotic postmenopausal women. Pamidronate is available for intravenous therapy and ibandronate and **zoledronate** may also become available for injection. Current research studies are examining new compounds, treatment regimens and the combination of bisphosphonates with other drugs such as oestrogen, which currently remains the first-line therapy for the prevention and treatment of osteoporosis in women.

L11 ANSWER 11 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2000137835 EMBASE

TITLE: [Bisphosphonates in oncology].
LES BISPHOSPHONATES EN CANCEROLOGIE.

AUTHOR: Paule B.; Clerc D.; Brion N.

CORPORATE SOURCE: B. Paule, Unite de Therapeutique, Centre Hospitalier de Versailles, 177, rue de Versailles, F 78157 Le Chesnay Cedex, France

SOURCE: Presse Medicale, (8 Apr 2000) Vol. 29, No. 13, pp. 723-729.

Refs: 81

ISSN: 0755-4982 CODEN: PRMEEM

COUNTRY: France

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
033 Orthopedic Surgery
037 Drug Literature Index

LANGUAGE: French

SUMMARY LANGUAGE: English; French

ENTRY DATE: Entered STN: 4 May 2000

Last Updated on STN: 4 May 2000

AB Mechanism of action: Tumor-induced osteolysis or lytic bone disease is mediated by osteoclast activation. Bisphosphonates inhibit bone resorption by reducing osteoclastic activity. Indications: Bisphosphonates were shown to be effective in treating cancer-related hypercalcemia. Recent large randomized clinical trials have shown the efficacy of bisphosphonates in reducing bone pain, pathological **fractures** and spinal cord compression for patients with multiple myeloma and breast cancer metastatic to bone. The potential survival benefit from pamidronate in patients with advanced myeloma warrants further study. Future: Future clinical trials will use more potent bisphosphonates (**zoledronate**, ibandronate) with the ultimate goal of trying to prevent bone metastases.

L11 ANSWER 12 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1999363604 EMBASE

TITLE: [Bisphosphonates and bone metastases].
BISPHOSPHONATES ET METASTASES OSSEUSES.

AUTHOR: Lortholary A.; Jadaud E.; Berthaud P.

CORPORATE SOURCE: A. Lortholary, Centre Paul-Papin, 2, Rue Moll, 49033 Angers, France

SOURCE: Bulletin du Cancer, (1999) Vol. 86, No. 9, pp. 732-738. .

Refs: 51

ISSN: 0007-4551 CODEN: BUCABS

COUNTRY: France

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: French
SUMMARY LANGUAGE: English; French
ENTRY DATE: Entered STN: 4 Nov 1999
Last Updated on STN: 4 Nov 1999

AB Bisphosphonates, potent inhibitors of bone resorption have been emerging as the standard treatment of tumor-induced hypercalcemia during the 90's. All uncontrolled phase II studies up to 1992 had demonstrated efficacy in reducing morbidity in terms of bone pain, **fracture** and hypercalcemia. Other studies on intravenous bisphosphonates, with no other anti-tumor treatment, even demonstrated sclerosis of osteolytic breast cancer bone metastases. Randomised phase III studies only began after 1992. In multiple myeloma, one study with oral clodronate has reported a decrease in bone events and two other studies, one with intravenous pamidronate and the other with oral clodronate have both reported a decrease in skeletal events and bone pain. In breast cancer patients with bone metastases, five large studies have been reported: three with intravenous pamidronate, one with oral pamidronate and one with oral clodronate. All these studies have demonstrated the superiority of bisphosphonates over placebo on both bone pain and bone events, but have failed to show an increase in duration of survival. Bisphosphonates should therefore be considered as an important part of the palliative treatment in breast cancer patients with bone metastases. On the other hand, no definite conclusion can be drawn on the role of bisphosphonates in the treatment of prostatic carcinoma bone metastases yet. However, bisphosphonates should be considered as part of the standard therapy in managing painful lesions in patients with multiple myeloma, breast cancer and prostatic cancer. Nevertheless, further studies are needed with bisphosphonates in the adjuvant setting before bone metastases appear. Could new and more potent bisphosphonates such as **zoledronate** further reduce bone metastases morbidity?.

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